EXHIBIT A11

Genital use of talc and risk of ovarian cancer: a meta-analysis

Wera Berge[a], Kenneth Mundt[b], Hung Luu[c] and Paolo Boffetta[d]

Some epidemiological studies suggest an association between genital use of talc powders and increased risk of ovarian cancer, but the evidence is not consistent. We performed a meta-analysis of epidemiological studies to formally evaluate this suspected association. A systematic search was conducted in Medline, Embase, and Scopus, leading to the identification of 24 case–control studies and three cohort studies. In the meta-analysis, we used a random-effect model to calculate summary estimates of the association between genital use of talc and occurrence of ovarian cancer. We assessed potential sources of between-study heterogeneity and presence of publication bias. The summary relative risk (RR) for ever use of genital talc and ovarian cancer was 1.22 [95% confidence interval (CI): 1.13–1.30]. The RR for case–control studies was 1.26 (95% CI: 1.17–1.35) and for cohort studies was 1.02 (95% CI: 0.85–1.20, $P_{heterogeneity}=0.007$). Serous carcinoma was the only histologic type for which an association was detected (RR: 1.24; 95% CI: 1.15–1.34). There was a weak trend in RR with duration and frequency of genital talc use. This meta-analysis resulted in a weak but statistically significant association between genital use of talc and ovarian cancer, which appears to be limited to serous carcinoma with suggestion of dose-response. The heterogeneity of results by study design however, detracts from a causal interpretation of this association. *European Journal of Cancer Prevention* 27:248–257 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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[a]Faculty of Medicine, University of Dresden, Dresden, Germany, [b]Ramboll Environ, Amherst, Massachusetts, [c]University of South Florida College of Public Health, Tampa, Florida and [d]Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, USA

Correspondence to Paolo Boffetta, MD, MPH, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, One Gustave L. Levy Place, Box 1130, New York, NY 10029, USA
Tel: + 1 212 824 7378; fax: + 1 212 849 2566; e-mail: paolo.boffetta@mssm.edu

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Introduction

With over 22 000 new cases diagnosed and about 14 000 deaths every year in the USA alone, ovarian cancer ranks as the fifth as a cause of neoplastic death among women. It accounts for more deaths than from any other cancer of the female reproductive system, although incidence numbers decreased since the mid-1980s (American Cancer Society, 2016). Most ovarian cancers are detected at a later stage and have limited prospects of cure. This is mainly because of the lack of a screening method for its detection at an early stage and resistance against chemotherapy. The etiology of the disease is not fully understood, although researchers have identified several risk factors, including a family history of ovarian or breast cancer, advanced age, white race, nulliparity, obesity, education level, and endometriosis (Kim *et al.*, 2014). In addition, breast feeding, tubal ligation, and oral contraceptive use have been reportedly associated with reduced risk (Webb *et al.*, 2008). Ovarian cancer is a heterogeneous disease that comprises four major histologic types; serous carcinoma is the most common form (50%), followed by mucinous, endometrioid, and clear cell carcinoma. Each type, with the exception of clear cell carcinoma, is divided into grades of malignancy (Wang *et al.*, 2005). On the basis of limited data, there appears to be some heterogeneity in risk factors for specific histologic types (Chiaffarino *et al.*, 2007; Gates *et al.*, 2010).

An association between exposure to asbestos and increased risk of ovarian cancer has been reported (Reid *et al.*, 2011), but it remains unclear whether this might reflect misclassification of peritoneal mesothelioma, a disease linked to high exposure to asbestos, or direct action of asbestos fibers on the ovary (Merino, 2010).

Talc is a naturally occurring mineral that is commonly used in bath and body powders as well as other cosmetic products. Talc naturally occurs as soft crystals that give it a soft, slippery feel, absorbency, softness, and resistance to clumping. It is often applied to sanitary napkins, condoms, or underwear, as well as directly to the genital area. To our knowledge, accurate estimates of prevalence of cosmetic talc use in the genital area are not available. However, the use of powders for female hygiene, including body or deodorizing powders containing cosmetic talc has been reported to be as high as 50% in some regions (International Agency for Research on Cancer (IARC), 2010), including parts of North America, Australia, and the UK.

Since 1982, when the first case–control study reported an association between genital talc and ovarian cancer, interest in genital talc use and risk of ovarian cancer has

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grown (Cramer *et al.*, 1982). The use of talcum powder in the genital area had been suggested as a potential risk factor for ovarian cancer based, in part, on a possible structural analogy with asbestos (Cramer *et al.*, 1982) or the possible contamination by asbestos of some talcum powders in the past (Cralley *et al.*, 1968). However, the structural similarities between asbestos minerals in the crystalline fiber form (i.e. asbestos habit) and structures seen microscopically in talcum that resemble fibers such as 'ribbons' of talc crystals or cleavage fragments of talc or other minerals, are few. Furthermore, talcum powders for domestic use in the USA have been virtually asbestos-free since the 1970s (Rohl *et al.*, 1976).

Several more recent case–control studies have reported associations between ovarian cancer and self-reported genital talcum powder use. However, the association between talc use and ovarian cancer risk reported in case–control studies has not been limited to studies in which genital talcum powder use occurred before cosmetic products were known to be asbestos-free. It has been suggested that talcum powder may be directly carcinogenic to the ovaries, provided that talc particles may be able to travel through the female reproductive system to the ovaries (Heller *et al.*, 1996). In one study, talc-like particles were detected more frequently in ovarian tumors than in normal human ovarian tissue, although the authors of this study emphasized that this study could not determine whether these particles actually caused the malignancy (Henderson *et al.*, 1979).

Results of epidemiological studies reported during the last three decades have not been consistent (Huncharek *et al.*, 2007; Terry *et al.*, 2013; Houghton *et al.*, 2014). It remains unclear whether a statistical association exists, and, if so, whether it can be interpreted as reflecting some form of bias or a causal relationship. We performed a systematic review and meta-analysis aiming at providing stronger evidence in favor or against the hypothesis of a causal association between genital talc use and risk of ovarian cancer.

Methods

We performed a systematic review and meta-analysis on the association between genital talc powder use and the risk of ovarian cancer. Our work was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Liberati *et al.*, 2009). A study protocol was developed in advance, outlining the procedure and methods (available upon request).

Search strategy

A series of literature searches was conducted in June 2016 using the electronic databases Medline (by PubMed), Embase, and Scopus. There was no limitation on year of publication. We included relevant studies that met the following criteria: papers had to be published in peer-reviewed journals as an original report; had to present novel information on the relation between genital powder use and ovarian cancer, and had to be written in English, German, Italian, French or Spanish. As there are different types of genital powders, we defined genital powder as any type of powder that is applied to the genital, rectal or perineal area, such as talc, baby, deodorizing, cornstarch, or powder of unknown type. We excluded review articles, abstracts, editorials or letters to the editor not including original data, and other studies not meeting the selection criteria.

The following keywords were used for the searches on Medline and Scopus: 'perineal powder' or 'talcum powder' or 'genital powder' and 'ovarian cancer.' For Embase we used the following combination of keywords: 'perineum' or 'talc' and 'ovarian cancer.' In addition, all references cited in the identified papers and reviews were hand-searched for potentially relevant studies that were not captured by the electronic database search.

Study selection

Titles and abstracts were examined independently by two of the authors (W.B., P.B.). Duplicates and irrelevant references were eliminated. In case of disagreement or doubt the abstracts or articles were discussed until consensus was reached. In case of overlap of results between publications the selection of results was on the basis of the largest population or most detailed analysis, resulting in the exclusion of some publications which were superseded by more recent reports (Harlow *et al.*, 1992; Cramer *et al.*, 1999; Pike *et al.*, 2004).

Data extraction

All data of the included studies were extracted by one author (W.B.) and checked by another author (P.B.). Possible disagreements were discussed and solved.

The following data were extracted from each study for the meta-analysis: first author and publication year; study design; study region; period of enrollment; survey instrument; assessment of ovarian cancer; age range; numbers of women with ovarian cancer and those without in case–control studies; numbers of cases of ovarian cancer, sample size and a number of person-years in cohort studies; adjustment for potential confounding factors; outcome by talc exposure (yes/no); duration (years); frequency (times/week); timing of use (early/late); type of talc exposure (sanitary napkin, diaphragm, genital deodorant, cornstarch, use by the partner); endometriosis; surgery (hysterectomy and/or tubal ligation); number of powder applications; characteristics of the participants; and tumor histology and behavior.

Quality assessment

Every included article was scored for its quality according to a standardized checklist. We used the Newcastle–Ottawa Scale (NOS) case–control checklist and the NOS cohort study checklist for both study types, respectively (Stang,

2010). The NOS assesses three dimensions of quality: selection, comparability, and exposure (for a case–control study) or outcome (for a cohort study). It assigns a maximum of four points for selection, two points for comparability, and three points for exposure or outcome. Studies with at least seven points were considered of high quality (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJCP/A138* and Table 2, Supplemental digital content 2, *http://links.lww.com/EJCP/A139*).

Statistical analyses

The measure of association of interest was the relative risk (RR) for prospective cohort studies, and the odds ratio (OR) for the case–control studies, with corresponding 95% confidence intervals (CIs). The main meta-analysis compared ever versus never use of genital talc; additional analyses addressed use of powder on sanitary napkins and diaphragms, two potential sources of talc exposure. If results were reported only by categories of exposure, indicators of ever talc use were derived using fixed-effect meta-analyses. Risk estimates were abstracted from each study for comparable exposure categories. An overall pooled RR was then estimated, together with its 95% CI, on the basis of individual estimates from each study. Each study was given a weight on the basis of the inverse of the variance of the effect estimate. We pooled data on different exposures when at least four studies provided sufficient data. A random-effects model was used in the meta-analyses comprising multiple studies, because of the heterogeneity in study design and analysis (DerSimonian and Laird, 1986). The I^2-statistic was used to assess the percentage of between-study variability that is because of heterogeneity rather than chance (Higgins *et al.*, 2003).

Stratified meta-analyses were conducted for ever genital use of talc according to study design (case–control vs. cohort studies), as well as tumor histology and behavior. Because of the fact that cosmetic talc may have been contaminated by asbestos before the 1970s, when voluntary guidelines were adopted, we compared the results on use in an 'early' and in a 'late' period: the exact cut-point varied across the studies but in general referred to 1970 or 1980.

Meta-regression analyses were performed to obtain overall risk estimates for duration (RR for 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency), for the studies reporting at least three categories of duration or frequency of use. Study-specific slopes were first derived from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model.

The presence and extent of publication bias were assessed visually using funnel plots and evaluated statistically using the Egger's test (Egger *et al.*, 1997). A cumulative meta-analysis was also performed by repeating the calculation of the summary RR and CI (on the basis of a random-effects model) each year a new study was published. When an article superseded a previous article from the same study, the results reported in the earlier report were replaced by the new results.

Analyses were performed using the commands *metan*, *glst*, *metafunnel*, and *metabias* of the statistical software STATA, version 14 (StataCorp, 2015).

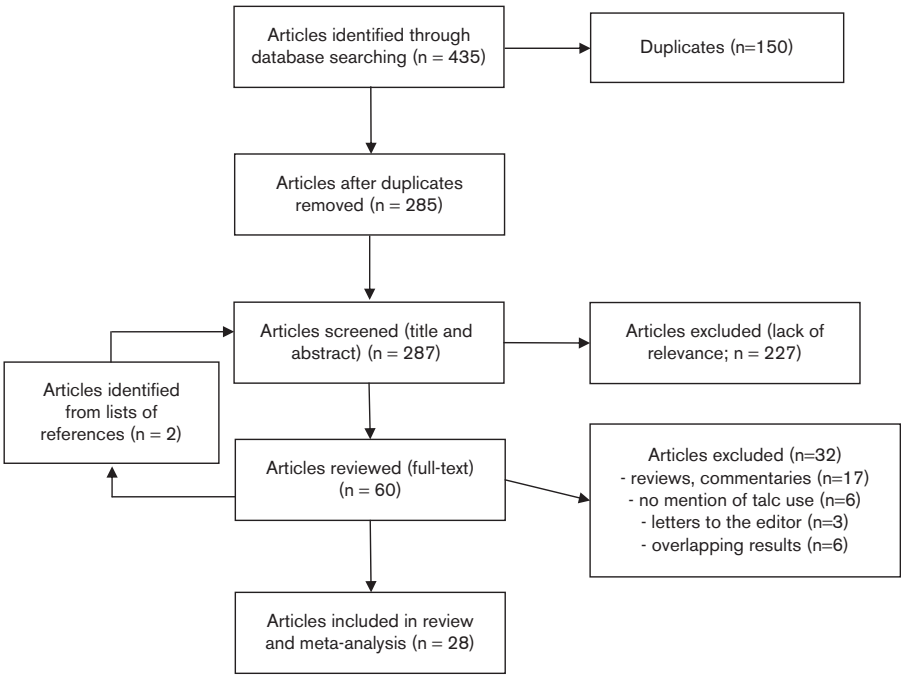
Results

The process of selection of relevant studies is shown in Fig. 1. The electronic searches resulted in a total of 435 articles, of which 150 overlapped between searches. After the exclusion of the duplicates and the addition of two articles identified through the review of the lists of references of eligible articles, we screened the titles of abstracts of 287 articles, and excluded 227 which appeared not to be relevant. We then reviewed the full text of the remaining 60 articles, and excluded 32 (17 commentaries, reviews or meta-analysis; three letters to the editor without original results, six reports of studies of ovarian cancer without results on talc use, and six articles whose results were superseded by subsequent publications). The remaining 28 articles, comprising three cohort studies, 24 case–control studies, and one pooled analysis of eight of the 24 case–control studies, were included in the review and meta-analysis.

Table 1 shows selected characteristics of the 28 articles included in the review, which provided the 27 risk estimates included in the meta-analysis [the pooled analysis (Terry *et al.*, 2013) did not provide an independent risk estimate]. For three of the case–control studies included in the pooled analysis (Goodman *et al.*, 2008; Moorman *et al.*, 2009; Lo-Ciganic *et al.*, 2012) results on genital talc use had not been reported in the original publications and were abstracted from the pooled analysis (Terry *et al.*, 2013). Twenty studies were conducted in the USA, two in Australia, two in Canada, one in Great Britain, one in China, and one in Greece. Potential confounding factors including age, parity, history of tubal ligation or hysterectomy, and use of oral contraceptive were adjusted for in most studies, although there were differences in the specific adjustments across studies. Six of the 24 case–control studies were hospital-based with the remainder being population-based.

The results of the meta-analysis are reported in Table 2. We used the results reported in the meta-analysis by Terry *et al.* (2013) for six of the original eight studies (Chang and Risch, 1997; Goodman *et al.*, 2008; Merritt *et al.*, 2008; Moorman *et al.*, 2009; Rosenblatt *et al.*, 2011; Lo-Ciganic *et al.*, 2012), while for the remaining two studies (Cramer *et al.*, 1999; Pike *et al.*, 2004) we used the more extensive results reported in subsequent publications (Wu *et al.*, 2015; Cramer *et al.*, 2016).

Fig. 1



Flow chart for the selection of studies to include in the meta-analysis.

The meta-analysis of all 27 risk estimates for ever use of genital talc yielded a summary RR of 1.22 (95% CI: 1.13–1.30). The forest plot of these results is shown in Fig. 2. When the meta-analysis was stratified according to study design, an association with ever genital talc use was detected in case–control studies (RR: 1.26; 95% CI: 1.17–1.35), but not in cohort studies (RR: 1.02; 95% CI: 0.85–1.20). The *P*-value of the test for heterogeneity of results according to study design was 0.007. Furthermore, hospital-based case–control studies resulted in a higher summary RR than community-based case–control studies ($P = 0.3$, for heterogeneity between the two groups of case–control studies).

The meta-analysis stratified by tumor behavior did not reveal a difference between results for borderline (RR: 1.27; 95% CI: 1.09–1.44) and invasive ovarian cancer (RR: 1.20; 95% CI: 1.08–1.31). The analysis stratified by histology, however, identified an association between ever genital use of talc and serous carcinoma (RR: 1.24; 95% CI: 1.15–1.34, on the basis of 13 case–control studies and no cohort studies). No significant associations were detected for endometrial (RR: 1.15; 95% CI: 0.91–1.39), mucinous (RR: 0.96; 95% CI: 0.73–1.18) or clear cell (RR: 0.98; 95% CI: 0.72–1.23) carcinomas. The *P*-value of the test of heterogeneity between histologic types was 0.04. Only two cohort studies reported histology-specific results, showing neither a difference between types nor stronger association for serous carcinoma (results not shown in detail). Three of the studies (Mills *et al.*, 2004; Rosenblatt *et al.*, 2011; Cramer *et al.*, 2016) reported results for serous carcinoma stratified by tumor behavior: they did not suggest any difference (RR = 1.39, for borderline serous carcinoma; 95% CI: 1.04–1.74; RR: 1.32, for invasive serous carcinoma; 95% CI: 0.97–1.67; $P_{\text{heterogeneity}} = 0.5$).

Use of talcum powder in the 'early' period showed weakly increased risk of ovarian cancer (RR: 1.18; 95% CI: 0.99–1.37), whereas the RR for use in the 'late' period was slightly higher but less precisely estimated (RR: 1.31; 95% CI: 1.03–1.61). The *P*-value of the test for heterogeneity between groups of studies was 0.37.

Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR: 1.00; 95% CI: 0.84–1.16; and RR: 0.75; 95% CI: 0.63–0.88, respectively).

We conducted additional analyses after stratifying the studies according to whether the results were adjusted for key potential confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/education, BMI; see Table 1 for details), but found no evidence of heterogeneity (results not shown in detail).

The results of the analysis by duration and frequency of genital talc use are reported in Table 3. A 10-year increase in genital talc use was associated with a RR of 1.16 (95% CI 1.07-1.26; 12 studies), whereas the RR for

Table 1 Selected characteristics of the studies included in the meta-analysis

References	Country	Study type	Age range	N ca/co	Potential confounders	Inclusion in meta-analyses	Overlap between publications
Cramer *et al.* (1982)	USA	CCC	18–80	215/215	Pa, MS	E, N, D	
Hartge *et al.* (1983)	USA	HCC	NA	135/171	–	E, D	
Whittemore *et al.* (1988)	USA	HCC	18–74	188/539	Pa, OC	E, N, D, Du, F	
Booth *et al.* (1989)	UK	HCC	20–64	235/451	SES	E, F	
Harlow and Weiss (1989)	USA	CCC	20–79	116/158	Pa, OC	E, N, D	
Chen *et al.* (1992)	China	CCC	NA	112/224	Pa, Ed	E	
Harlow *et al.* (1992)	USA	CCC	18–76	235/239	Pa, Ed, MS, BMI	E, H, B, F, Du, T, N, D	
Rosenblatt *et al.* (1992)	USA	HCC	All	77/46	–	E, N, D	
Tzonou *et al.* (1993)	Greece	HCC	< 75	189/200	Pa, Ed, BMI, AMe, MS, AFB, Tob, Cof, Alc, Med, HD	E	
Purdie *et al.* (1995)	Australia	CCC	18–79	824/860	Pa	E	
Chang and Risch (1997)	Canada	CCC	35–79	450/564	OC, NPr, BF, TL, Hys, FH	Du, T, N	Included in Terry *et al.* (2013)
Cook *et al.* (1997)	USA	CCC	20–79	313/422	–	E, H, Du, N, D	
Godard *et al.* (1998)	Canada	CCC	20–84	170/170	–	E	
Wong *et al.* (1999)	USA	HCC	NA	499/755	Pa, OC, Tob, FH, AMe, MS, Inc, Ed, TL, Hys	E, Du, N	
Ness *et al.* (2000)	USA	CCC	20–69	767/1367	NPr, FH, OC, TL, Hys, BF	E, Du, N, D	
Mills *et al.* (2004)	USA	CCC	18 +	256/1122	OC, BF	E, H, B, F, Du, T	
Goodman *et al.* (2008)	USA	CCC	18 +	367/602	NA		Included in Terry *et al.* (2013)
Merritt *et al.* (2008)	Australia	CCC	18–79	1576/1509	Pa, Ed, OC	Du	Included in Terry *et al.* (2013)
Moorman *et al.* (2009)	USA	CCC	20–74	1086/1057	–		Included in Terry *et al.* (2013)
Gates *et al.* (2010)	USA	Cohort	30–55	721/–	Pa, BMI, PA, Tob, FH, BF, OC, TL, Hys, Amp, HRT	E, H, F[a], N[a]	
Rosenblatt *et al.* (2011)	USA	CCC	35–74	812/1313	NPr, OC	Du, T, N, D	Included in Terry *et al.* (2013)
Lo-Ciganic *et al.* (2012)	USA	CCC	25 +	902/1802	NA		Included in Terry *et al.* (2013)
Terry *et al.* (2013)	USA, Canada, Australia				Pa, OC, TL, BMI	E, H, B	Pooled data from Chang and Risch (1997), Goodman *et al.* (2008), Moorman *et al.* (2009), Rosenblatt *et al.* (2011), Lo-Ciganic *et al.* (2012), Merritt *et al.* (2008)
Houghton *et al.* (2014)	USA	Cohort	50–79	429/–	Pa, OC, HRT, FH, ALB, BMI, Tob, TL	E, H, N, D, DU	
Wu *et al.* (2015)	USA	CCC	18–74	1701/2391	MS, AMe, HRT, BMI, Inc, Ed, NPr, OC, TL, End, FH	E, T[b]	
Cramer *et al.* (2016)	USA	CCC	18–80	2041/2100	–	E, H, B, F, Du, D	
Gonzalez *et al.* (2016)	USA, Puerto Rico	Cohort	35–74	154/–	BMI, OC, MS, TL, Hys	E	
Schildkraut *et al.* (2016)	USA	CCC	20–79	584/745	Pa, Ed, OC, BMI, TL, FH	E, H, Du, F	

N ca/co, number of cases and controls (only cases for cohort studies).

AFB, age at first birth; ALB, age at last birth; AMe, age at menarche; AMp, age at menopause; B, tumor behavior; BF, breast feeding; CCC, community-based case–control study; D, diaphragm use; Du, duration of use; E, ever use; Ed, education; F, frequency of use; FH, family history of breast and ovarian cancer; H, histologic type; HCC, hospital-based case–control study; HD, hair dye use; HRT, hormone replacement therapy; Hys, hysterectomy; Inc, income; Med, use of medications; MS, menopausal status; N, sanitary napkin use; NA, not available; NPr, number of pregnancies; OC, oral contraceptive use; Pa, parity; SES, socioeconomic status; T, timing of use; TL, tubal ligation.

[a]Results abstracted from Gertig *et al.* (2000).

[b]Results abstracted Wu *et al.* (2009).

Table 2 Ever use of genital talc – results of meta-analysis

	Number of risk estimates	RR	95% CI	p-het
Overall	27	1.22	1.13–1.30	0.02
Study design				
Cohort studies	3	1.02	0.85–1.20	0.2
Case–control studies	24	1.26	1.17–1.35	0.08
Hospital-based case–control studies	6	1.34	1.16–1.51	0.8
Community-based case–control studies	18	1.24	1.13–1.35	0.03
Histology				
Serous carcinoma	13	1.24	1.15–1.34	0.4
Mucinous carcinoma	12	0.96	0.73–1.18	0.8
Endometrial carcinoma	12	1.15	0.91–1.39	0.1
Clear cell carcinoma	8	0.98	0.72–1.23	0.8
Behavior				
Invasive	9	1.20	1.08–1.31	0.2
Borderline	9	1.27	1.09–1.44	0.9
Period of exposure[a]				
Early	5	1.18	0.99–1.37	0.2
Late	5	1.31	1.03–1.61	0.2
Specific sources of talc exposure				
Sanitary napkin	12	1.00	0.84–1.16	0.5
Diaphragm	11	0.75	0.63–0.88	0.8

CI, confidence interval; p-het, *P*-value of test for interstudy heterogeneity; RR, relative risk.
[a]Cut-points between periods vary across studies but in general refer to 1970 or 1980.

an increase of one application per week was 1.05 (95% CI 1.04-1.07; 7 studies).

The funnel plot of the results of ever genital talc use is shown in Fig. 3. Visual inspection of the plot suggests no serious publication bias: this conclusion is supported by the result of the Egger test ($P = 0.7$). The results of the cumulative meta-analysis (Fig. 4) suggest that after the publication of a few initial studies with inconsistent results, the summary RR stabilized with values in the range of 1.20–1.25.

Discussion

Ovarian cancer, unless diagnosed and treated early, remains a highly lethal disease and the identification of modifiable risk factors is an important component of the strategy for its control. The primary aim of this meta-analysis was to determine whether talcum powder use in the female genital area is a potential risk factor for ovarian cancer. Previous meta-analyses (Huncharek *et al.*, 2003; Langseth *et al.*, 2008) were only on the basis of a fraction of currently available studies, and had limited ability to explore potential sources of heterogeneity in results.

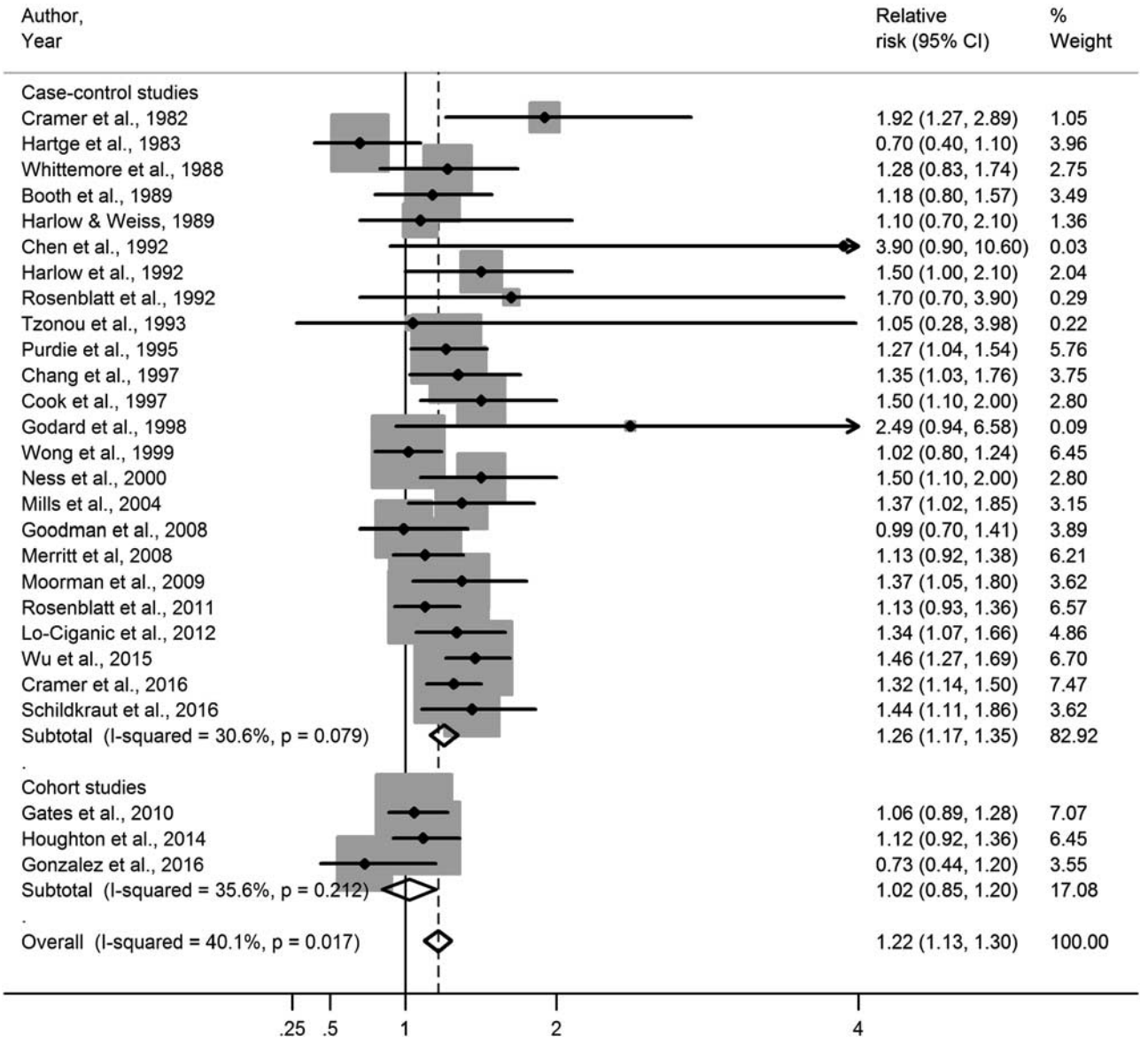
This meta-analysis suggests that genital powder use is associated with a small increased risk of developing ovarian cancer; however, this positive association appears to be limited to the serous histologic type, and to case–control studies. This estimate is somewhat lower than that of previous meta-analyses (Huncharek *et al.*, 2003; Langseth *et al.*, 2008): in our cumulative meta-analysis we confirmed the trend toward lower overall risk estimates as more evidence accumulated.

An important feature of the present meta-analysis is the inclusion of several cohort studies, which enabled an analysis stratified by study design. This analysis provided evidence of heterogeneity of results between the two groups of studies, with an association generally detected in case–control studies but not in cohort studies. It should be noted that the cohort studies included in the meta-analysis comprised a total of 429 cases of ovarian cases exposed to genital talc and 943 unexposed cases: the statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case–control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as explanation of the heterogeneity of results.

The fact that the association between genital talc use and risk of ovarian cancer is present in case–control, but not in cohort studies, can be attributed to bias in the former type of studies (Kopec and Esdaile, 1990; Rothman *et al.*, 2008). Selection bias might have played a role in the results of some of the case–control studies (e.g. those with low response rate, or those hospital-based, which resulted in a nonsignificantly higher summary risk estimate than community-based studies); in addition, information bias from retrospective self-report of talc use is a possible explanation for the association detected in case–control studies. In particular, some of the most recent case–control studies (Cramer *et al.*, 2016; Schildkraut *et al.*, 2016) have reported particularly strong associations (RR >1.4) for ever use of talc. These results may have occurred at least in part because of participants' knowledge about the latest controversies about talc use and ovarian cancer risk spread by the media (Muscat and Huncharek, 2008).

The results of the analysis by histologic type of ovarian cancer pointed toward an association with serous carcinoma, but not with the other main types (i.e. endometrial, mucinous, and clear cell carcinoma). Several studies have suggested heterogeneity in risk factors of different histologic types, which are characterized by distinctive molecular and genetic profiles (Kurian *et al.*, 2005; Gates *et al.*, 2010; Gilks, 2010). However, no results are available on whether the association between asbestos exposure and ovarian cancer risk varies by histologic type (Camargo *et al.*, 2011; Reid *et al.*, 2011). The finding that the association between genital talc use and ovarian cancer may vary by histologic type detracts from the hypothesis of report bias as an explanation of the findings of case–control studies, as this type of bias would likely operate for all histologic types of the disease. Caution should however be warranted in the interpretation of these findings, as the test for heterogeneity between groups was of borderline statistical significance, and the evidence for heterogeneity derives only from case–control studies.

Fig. 2



Forest plot of results on ever use of genital talc and risk of ovarian cancer. CI, confidence interval.

Table 3 Duration and frequency of use of genital talc – results of meta-analysis

	Number of risk estimates	RR	95% CI
Duration (10 years)	12	1.16	1.07–1.26
Frequency (1 time/week)	7	1.05	1.04–1.07

CI, confidence interval; p-het, RR, relative risk.

The presence or absence of a dose–response is an important aspect to consider in assessing the plausibility of the causal nature of an association observed in a meta-analysis. The number of studies included in the analysis of duration and frequency of genital talc use was not very large, and the modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding, and analyses based on larger datasets would be required is a potentially important and novel contribution of this meta-analysis.

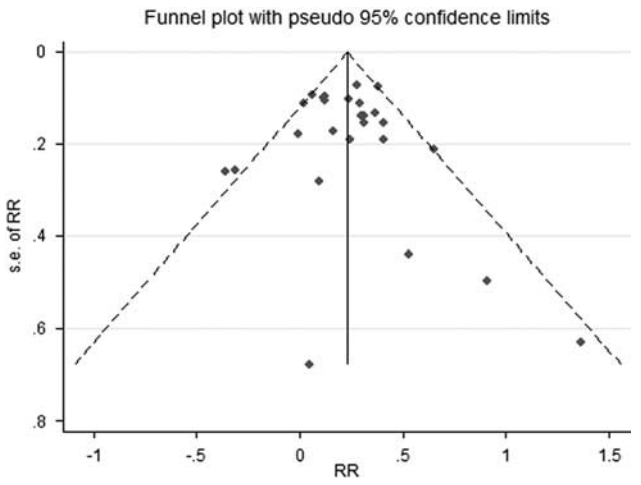
We aimed at analyzing the results on genital use of talc according to time-periods; this analysis was limited by different cut-points used by various authors to define time intervals of exposure. In general, however, we were able to distinguish an ‘early’ and a ‘late’ period, with the limit between the two running between 1970 and 1980, and we found a statistically significant association only for ‘late’ use. This result goes against the hypothesis that a stronger association (if any) would be seen among those

more likely to have used talcum powders in a time period in which contamination with asbestos fibers was possible (Rohl *et al.*, 1976).

Our study suffers from limitations common to meta-analyses of observational studies: neither the definition of the exposure of interest (genital talc use) nor the strategy for adjustment for potential confounders were fully consistent across studies. Also, there were limitations not specific to our study, including the self-reported information on the main exposure of interest, with no external validation data, the predominance of retrospective case–control studies, and the small number of studies providing results by histologic type or quantitative measures of genital talc use. It is difficult to assess the combined effect of the potential sources of bias, as they might have operated in different directions on the estimate of the association between talc use and ovarian cancer. The stratified analyses we conducted did not point toward the presence of residual confounding (i.e. higher risk estimates for unadjusted compared with adjusted results).

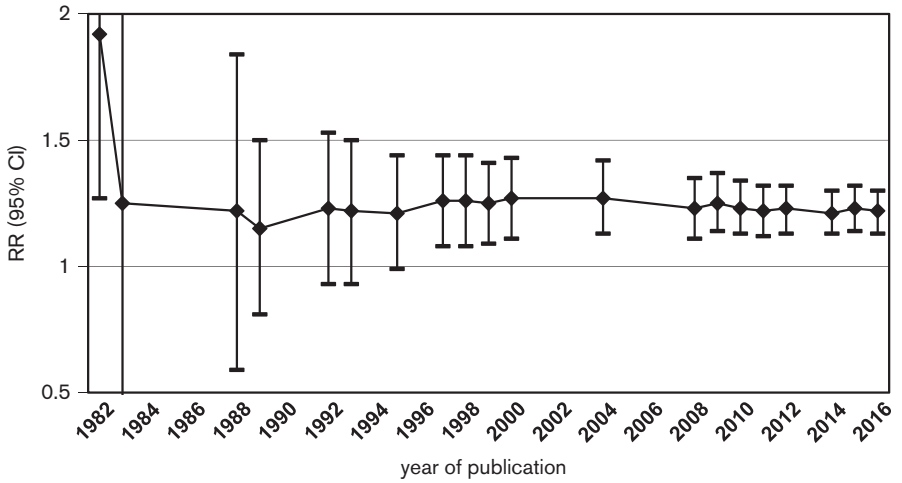
The biological basis and plausibility of a possible carcinogenic effect of talc on the ovaries is still not understood and remains questionable. The similarity of physicochemical characteristics of talc and asbestos has been proposed to explain a carcinogenic effect of the former (Cramer *et al.*, 1982). However, although both talc and various forms of asbestos minerals belong to the family of silicates, they are morphologically distinct. It is the fibrous form of asbestos which determines its carcinogenic potential (Stanton *et al.*, 1981; Huncharek, 1986; Mossman and Gee, 1989). Talc is not fibrous or crystalline (International Agency for Research on Cancer (IARC), 2010), and in-vitro studies have shown that talc is not genotoxic (Wehner, 1994). This is supported by the evidence that exposure to talc not contaminated with asbestiform fibers is not associated with increased risk of lung cancer or mesothelioma in occupational cohorts (International Agency for Research on Cancer (IARC), 2010). The occupational cohorts supporting this conclusion comprise mostly men, and therefore provide no evidence in favor or against the hypothesis of a role of occupational talc exposure as an ovarian carcinogen, but the likelihood that talc could selectively cause ovarian cancer but not lung cancer or mesothelioma at high concentrations in talc miners and millers appears to be low. Furthermore, there is no evidence that occupational exposure to talc, for example, in the pulp and paper

Fig. 3



Funnel plot of results on ever use of genital talc and risk of ovarian cancer. RR, relative risk.

Fig. 4



Cumulative meta-analysis of results on ever use of genital talc and risk of ovarian cancer. CI, confidence interval; RR, relative risk.

industry, entails an increased risk of ovarian cancer (Langseth and Kjaerheim, 2004).

In conclusion, our meta-analysis identified a small but statistically significant association between genital talc use and risk of ovarian cancer; however, this association was limited to the serous histologic type, and to case–control studies. The results by histologic type might argue for specificity of the association, in the absence, however, of a biologic rationale for an effect on serous carcinoma compared with other types. Several aspects of our results, including the heterogeneity of results between case–control and cohort studies, however, do not support a causal interpretation of the association.

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Conflicts of interest

There are no conflicts of interest.

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